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ORIGINAL ARTICLE

Comparative study of two radiotherapy regimens for palliation of symptomatic advanced non-small cell lung cancer

N.A. Eldeeb^a, A.M. Bela^a, A.A. Eganady^{b,*}, A.S. Radwan^a

^a *Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Alexandria University, Egypt*

^b *Chest Diseases Department, Faculty of Medicine, Alexandria University, Egypt*

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KEYWORDS

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Abstract *Introduction:* Lung cancer is the most commonly diagnosed cancer worldwide and causes approximately 1–2 million deaths per year. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases, presenting as locally advanced disease in approximately 25–30% of cases and as metastatic disease in approximately 40–50% of cases.

Aim of the work: To compare symptom control in patients with inoperable, locally advanced or metastatic NSCLC using two different regimens of palliative external beam radiotherapy (RT), and to determine toxicity profile, health related quality of life (HRQOL), tumor control, and overall survival.

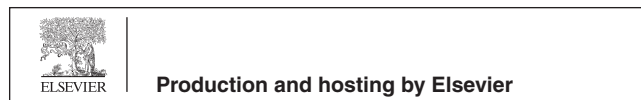
Patients and methods: A prospective clinical study included 30 patients who were randomly assigned into two groups; group (A) 15 patients received RT regimen of 10 fractions of 3 Gy over 2 weeks to a total dose of 30 Gy, and group (B) 15 patients received RT regimen of two fractions of 8.5 Gy days 1 and 8 to a total dose of 17 Gy. All patients in the study were subjected to the following: pretreatment evaluation, RT, patient's assessment, HRQOL, tumor control, and overall survival.

Results: The hypo fractionated RT regimens used in this study proved to be equally effective as the more protracted regimen in terms of palliation of the intrathoracic symptoms, treatment tolerance, HRQOL, and overall survival. This may hopefully convince at least some radiation oncologists still using more protracted regimens to adopt this simple and efficient treatment.

* Corresponding author. Tel.: +20 01223926049.

E-mail address: a.ganady@hotmail.com (A.A. Eganady).

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Conclusion: Palliative RT plays an important role of palliation of symptomatic intra thoracic disease and in preservation of HRQOL in patients who have limited expected survival time and or intolerance to combined chemotherapy and radical RT regimens.

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Introduction

Lung cancer is the most commonly diagnosed worldwide, and causes more deaths than any other cancer. In the year 2008, approximately 15% of new lung cancer in the United States will be diagnosed, with an estimated death rate of 31% in males and 26% in females [1]. In Egypt, however there is no population based cancer registry, but based on Gharbia cancer registry, lung cancer represents 5.1% of all incident cancers [2].

The treatment of NSCLC which represents 80% of all lung cancers is still a challenge for oncologists. In the past decade, combined-modalities treatment in stage III disease and chemotherapy for stage IV disease improved the survival and HRQOL. But unfortunately many patients are unfit to undergo these intensive treatments [3,4].

Consequently, a shorter course of hypo fractionated RT for palliation, if effective and unduly toxic, would be an attractive alternative to more protracted regimens, so clinical trial that is organized to ensure homogeneity in both patient characteristics and treatment interventions is needed. Shorter hypofractionated schedules require fewer trips to the RT facility for the patient, and in all likelihood, smaller directly and indirectly costs for society, especially for developing countries (like Egypt) with limited resources [4].

To measure the effect of palliative intervention, it is recommended to use patients' self-reported assessment using validated instruments but unfortunately, most reports regarding palliative fractionation in NSCLC have used clinical assessment of palliative effect only [5].

Aim of the work

Primary objective was to compare symptoms' control in patients with inoperable, locally advanced or metastatic NSCLC using two different regimens of palliative RT.

Secondary objective was to determine; toxicity profile, HRQOL, tumor control, and overall survival.

Patients

This was a prospective clinical study that included 30 patients, who were randomly assigned into one of two groups:

Group A: Consisted of 15 patients who received RT regimen of 10 fractions of 3 Gy over 2 weeks to a total dose of 30 Gy.

Group B: Consisted of 15 patients who received RT regimen of two fractions of 8.5 Gy days 1 and 8 to a total dose of 17 Gy. Conditions for Patient Eligibility:

1. Cytological proven diagnosis of NSCLC.
2. Inoperable Stage III or IV disease.
3. Age \geq 18 years.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) \geq 2 (Appendix I). [6]
5. Pulmonary symptoms attributable to the primary tumor.

6. Unfit for chemotherapy.
7. Patients with relapse in the chest after previous surgery.
8. Previous chemotherapy, but no earlier RT to the primary tumor.
9. No Prior invasive malignancy (except non-melanomatous skin cancer).
10. Signed study specific informed consent prior to study entry.

Methods

All patients in the study were subjected to the following:

Pretreatment evaluation

1. History taking and physical examination.
2. Current weight, height, and detection of the weight loss in the past six months.
3. Assessment of ECOG performance status [6].
4. Biopsy was performed by fiber optic bronchoscopy (FOB) or CT guided biopsy.
5. Staging workup including X-ray chest, CT chest, abdomen and pelvis.
6. Cerebral CT or MRI and bone scans were only performed when indicated.
7. Determination of tumor measurements.
8. Routine laboratory studies.
9. The patients were categorized according to the American Joint Committee on Cancer (AJCC) staging system [7]. Updated after the end of patients accrual.

Radiation therapy

RT was given with Mega-voltage linear accelerator with photon beams of \geq 6 MV.

Immobilization, simulation, and localization

- Patient setup was achieved by the use of customized immobilization devices.
- The patient position was supine with the arms above the head.
- A treatment planning CT scan for defining target volumes.
- Contrast use improved the contouring of centrally located tumors.
- The treatment isocenter was located in the tumor mass.

Treatment planning/target volumes

1. Gross Tumor Volume (GTV): included the gross primary tumor and the adjacent pathologically enlarged lymph nodes.

2. **Planning Target Volume (PTV):** represents an additional margin around GTV to compensate for the variability of treatment set up. A margin of 1.5–2 cm around the GTV was required in all directions to define the PTV.

Dose specifications

A total dose of 30 Gy (3 Gy/fraction) over 2 weeks in group A and 17 Gy (8.5 Gy/fraction) in group B was prescribed.

Co-medication

To prevent possible side effects from larger fractions, patients in group II were prophylactically administered (prednisolone, analgesics bronchodilators and oxygen).

Patient assessment

Symptom control

Patients' self-reported symptoms control. European Organization for Research and Treatment of Cancer (EORTC) lung cancer-specific module QLQ-LC13 (Arabic version) was used (Appendix I) [8]. The QLQ-LC13 module contains items for measuring dyspnea, cough, hemoptysis, mucositis, dysphagia, peripheral neuropathy, alopecia, pain, and analgesic consumption or effect. Mean scores for cough, hemoptysis, dyspnea, and chest pain were taken at base line, 1, 6 and 16 weeks after the end of RT. All these symptoms were linearly transformed to a scale from 0 to 100, with a higher score on the scale indicating a high degree of symptoms.

Clinicians' assessed symptoms control. Symptoms such as cough, hemoptysis, dyspnea, and dysphagia and chest pain were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Appendix III) [9] and recorded at baseline and at 1 week, 6 weeks, and 16 weeks after completing RT.

Toxicity profile

Patients' self-reported toxicity. This study used both the EORTC Quality of Life Questionnaire (QLQ)-C30 and the EORTC lung cancer-specific module QLQ-LC13 (Arabic versions) [8].

Clinicians' assessed toxicity. This study utilized the criteria of the CTCAE version 3.0 for grading of all adverse events [9]. It was assessed at the follow-up times.

Health related quality-of-life

This study used the EORTC Quality of Life Questionnaire (QLQ)-C30 [8].

Tumor control

Chest radiographs or CT chest scans to assess the tumor response within the RT fields were obtained at 6 weeks and/or 4 months after RT. These were categorized into five radiographic responses: complete response, partial response (tumor regression $\geq 50\%$), minor response (tumor regression $\geq 25\%$ but $< 50\%$), stable disease (no change in lesion size

or $< 25\%$ increase or decrease), and progressive disease (growth in irradiated volume of $\geq 25\%$) [4].

Overall survival

Was calculated from the date of study entry till the date of death, or lost follow up. It was estimated by Kaplan–Meier's method [10].

Statistical analysis of the data

Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed using Range, mean and standard deviation while Qualitative data were expressed in frequency and percent. Qualitative data were analyzed using Chi-square test also exact tests such as Fisher exact and Monte Carlo were applied to compare the two groups while, McNemar-Bowker was used to analyze the significance between the different stages. Quantitative data were analyzed using Mann Whitney test to compare between two groups. Wilcoxon Signed Rank test was used to compare between the different periods.

Results

Clinico pathological features

1. **Age:** In the whole series the age ranged between 30 and 80 years, with a mean age of 60.93 and 59.33 years for group A and group B, respectively.
2. **Gender:** Where 80% of the patients in group A were males and 93.3% of the patients in group B were males with no significant statistical difference.
3. **Smoking history and frequency:** The majority of patients in both groups were smokers; where 80% of patients in group A and 86.7% of patients in group B were smokers with no significant statistical difference.
4. **Performance status (P.S):** According to the ECOG scale the P.S of the majority of patients in both groups were 3 (73.3% and 53.3% of patients in group A and B, respectively) whereas 26.7% and 40.0% of patients in group A and B, respectively were 2 (Fig. 1).
5. **Presenting symptoms:** According to CTCAE. In group A the most significant symptoms grade ≥ 2 were cough, dyspnea, hemoptysis and chest pain with a frequency of 100%, 100%, 60% and 46.7%, respectively, whereas in group B the symptoms were also cough, dyspnea, hemoptysis and chest pain with a frequency of 100%, 93.3%, 66.7% and 66.6%, respectively (Table 1).
6. **Tumor characteristics:** As shown in Table 2 the majority of the patients incorporated in this study were of T₃ and T₄ lesions, as 60% of patients in group A were T₃ while 33.3% were T₄ and 46.7% of patients in group B were T₃ while 53.3% were T₄. Whereas only 1 patient in this study was T₂ and he was in group A. As regards the nodal status which was radiologically proved, N₂ lesions predominate in both groups and constituted 80% and 73.3% in group A and B, respectively.

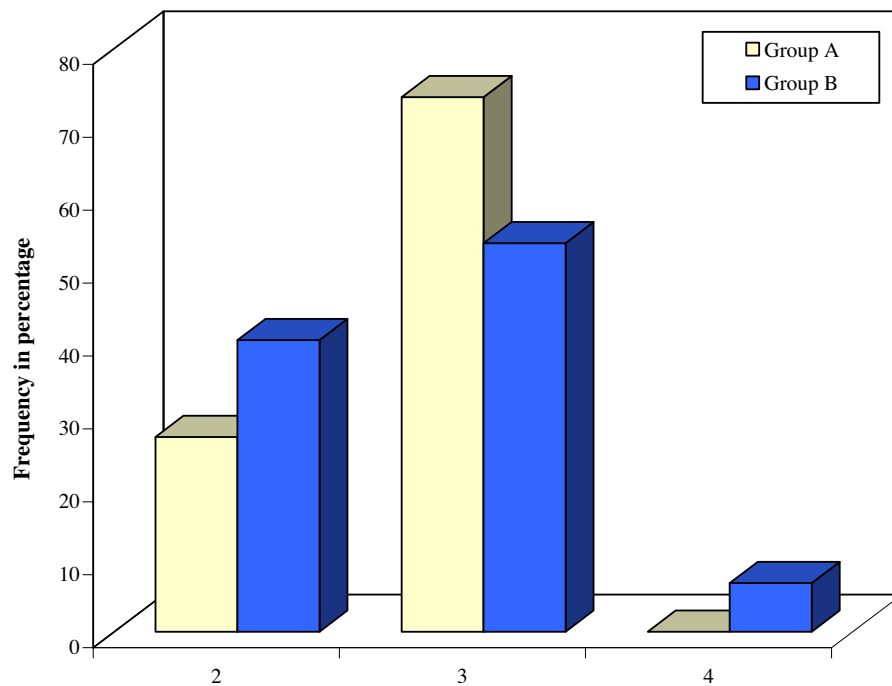


Figure 1 Comparison between the two studied groups according to Performance status.

Table 1 Presenting symptoms and weight loss among the studied groups.

	Group A (30 GY)		Group B (17 GY)		Test of significance
	No.	%	No.	%	
Dyspnea					MCp = 1.000
GI	0	0.0	1	6.7	
GII	5	33.3	6	40.0	
GIII	9	60.0	8	53.3	
GIV	1	6.7	0	0.0	
Hemoptysis					MCp = 0.743
Non	6	40.00	5	33.3	
GII	6	40.0	4	26.7	
GIII	2	13.3	5	33.3	
GIV	1	6.7	1	6.7	
Cough					FEp = 1.000
GII	5	33.3	4	26.7	
GIII	10	66.7	11	73.3	
Chest pain					MCp = 0.774
Non	2	13.3	1	6.7	
GI	6	40.0	4	26.7	
GII	3	20.0	5	33.3	
GIII	4	26.7	5	33.3	
Dysphagia					MCp = 0.221
Non	8	53.3	6	40.0	
GI	6	40.0	4	26.7	
GII	1	6.7	5	33.3	
Weight loss					FEp = 1.000
No	3	20.0	4	26.7	
Yes	12	80.0	11	73.3	

MCp, *p* value for Monte Carlo test; FEp, *p* value for Fisher Exact test.

Table 2 Tumor size, nodal status and TNM staging.

	Group A (30 GY)		Group B (17 GY)		Test of significance
	No.	%	No.	%	
Tumor size					MCp = 0.458
T2	1	6.7	0	0.0	
T3	9	60.0	7	46.7	
T4	5	33.3	8	53.3	
Nodal status					MCp = 1.000
N1	1	6.7	1	6.7	
N2	12	80.0	11	73.3	
N3	2	13.3	3	20.0	
Stage					MCp = 1.000
IIIA	2	13.3	2	13.3	
IIIB	4	26.7	5	33.3	
IV	9	60.0	8	53.3	
Brain	1	6.7	1	6.7	
Bone	1	6.7	0	0.0	
Liver	3	20.0	4	26.4	
Multiple site	1	6.7	1	6.7	
Suprarenal	3	20.0	2	13.3	

MCp, *p* value for Monte Carlo test.

7. Methods of obtaining biopsy: Most of the patients in both groups 66.7% were diagnosed through FOB biopsy. While the remaining 33.3% were diagnosed through CT guided biopsy.
8. Histopathological type: Squamous cell carcinoma was the commonest pathological type in both groups and represented 40% and 46.7% in group A and group B, respectively (Fig. 2).

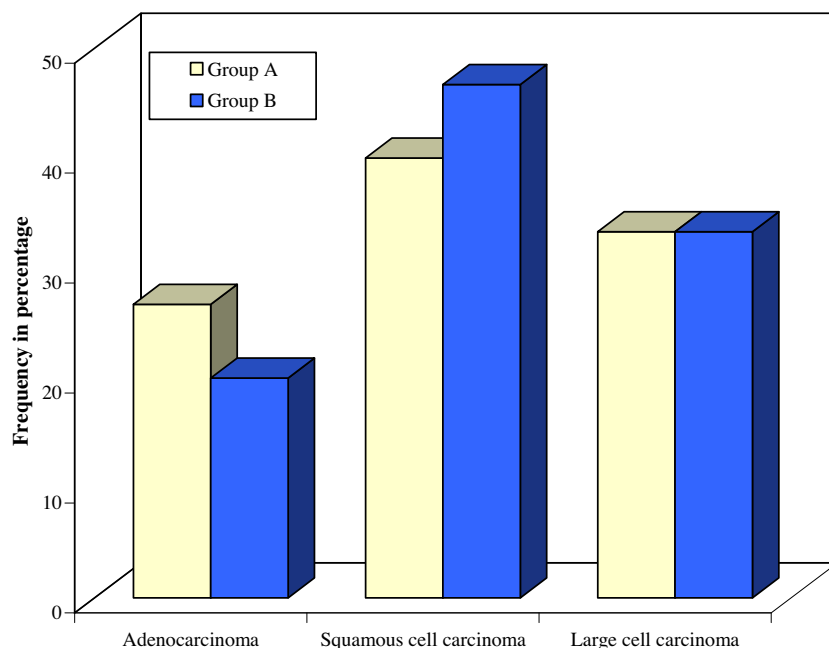


Figure 2 Comparison between the two studied groups according to Histopathology.

Table 3 Numbers of patients reporting symptomatic improvement after RT.

		Start		After 1 week	After 6 weeks	After 16 weeks	Overall improvement	
		No.	%				No.	%
Dyspnea	A	15/15	100.0	10/15	1/5	0/2	11/15	73.3
	B	15/15	100.0	8/15	1/7	0/4	9/15	60.0
	FEP						0.700	
Hemoptysis	A	9/15	60.0	9/9	–	–	9/9	100.0
	B	10/15	66.7	10/10	–	–	10/10	100.0
	FEP						–	
Cough	A	15/15	100.0	9/15	1/6	0/3	10/15	66.7
	B	15/15	100.0	11/15	0/4	0/2	11/15	73.3
	FEP						1.000	
Chest pain	A	9/15	53.3	6/9	0/3	0/0	6/9	66.7
	B	11/15	73.3	7/11	1/4	0/1	8/11	72.7
	FEP						1.000	

FEP, *p* value for Fisher Exact test.

9. Previous Chemotherapy: Eleven out of 15 patients in group A had received chemotherapy before study entry. As regards group B, 9 out of 15 patients had received previous doses of chemotherapy. All of the patients in both groups had received cisplatin based chemotherapy.

Symptoms control

Patients' self reported symptom control

100% of patients in both groups had reported palliation of hemoptysis, while dyspnea was improved in 73.3% and 60% of patients in group A and group B, respectively. Cough was palliated in 66.7% and 73.3% of patients in group A and group B, respectively. Symptomatic improvement of chest pain

was 66.7% and 72.7% of patients in group A and group B, respectively (Table 3).

Among both groups the mean scores of dyspnea, cough, and hemoptysis were improved significantly in the week 1, 6 and 16 following RT, with no statistically significant differences among the 2 groups; while the mean score of chest pain was improved significantly only in week 1 and 6 and worsened again in week 16, with no statistically significant differences between the 2 groups (Fig. 3).

Clinicians' reported symptom control

Hemoptysis had the highest improvement rate 100% in both groups which is noted at the first week after RT and seemed to last throughout the planned follow up period. Dyspnea was palliated in 10 (66.7%) out of 15 patients with significant

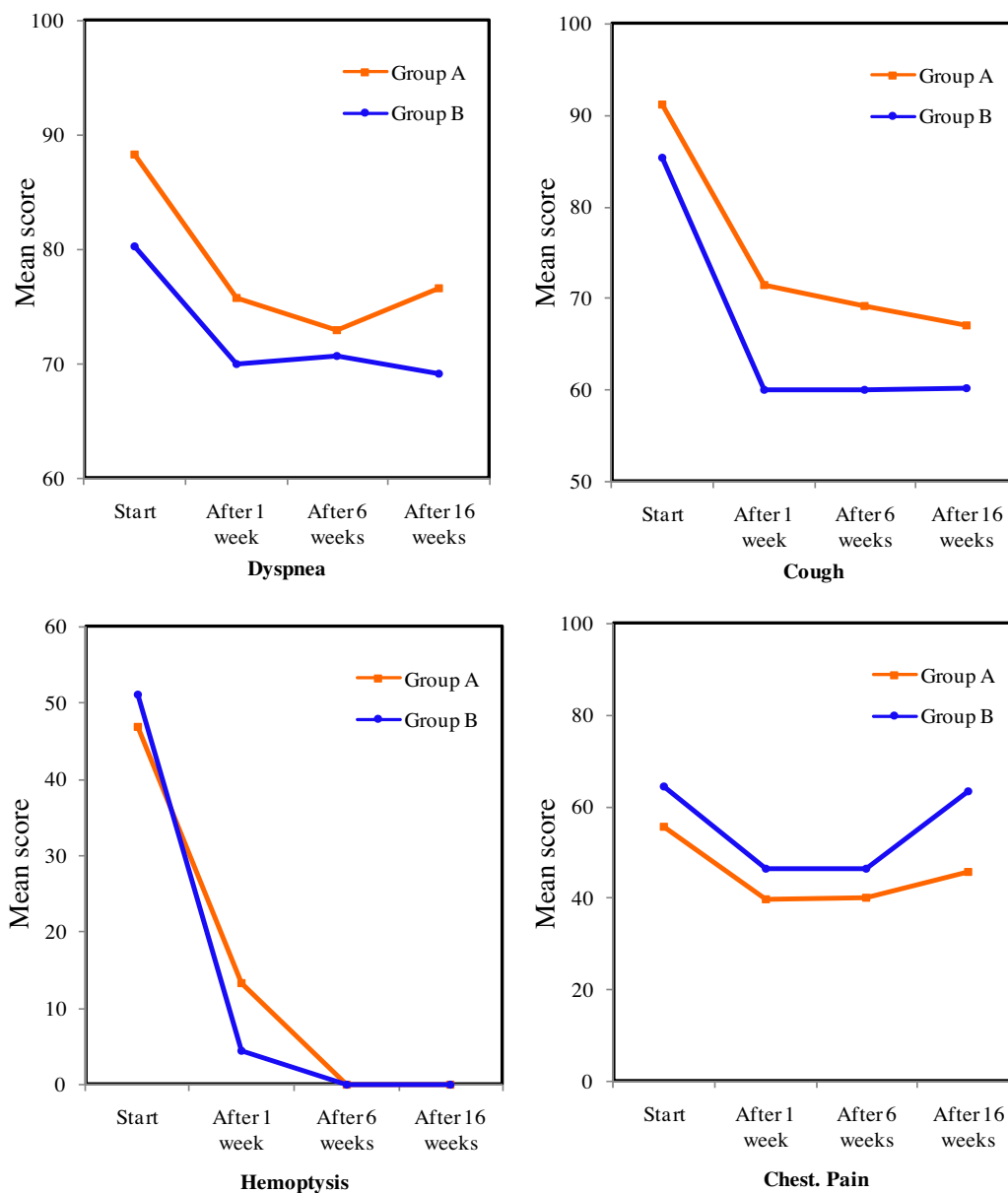


Figure 3 Comparison between the two studied groups according to patients' self reported symptom control.

dyspnea in group A. Specifically, dyspnea improved in 9 patients at the first week after RT and in 1 patient at the sixth week; while 9 (64.3%) out of 14 patients with significant dyspnea in group B were palliated, 6 of them at the first week after RT and 3 at the sixth week. Cough was improved in 9 (60%) out of 15 patients with significant cough in group A, 8 of them were improved at first week after RT and only 1 patient at the sixth week; while 10 (66.7%) out of 15 patients with significant cough in group B were palliated, all of them at the first week after RT. As regards patients with significant chest pain, in group A 5 (71.4%) out of 7 patients were palliated, all at the first week after RT; while in group B 7 (70%) out of 10 patients with significant chest pain were improved, all of them at the first week after RT (Table 4).

Toxicity

Patients' self-reported toxicity

Dysphasia is considered the main side effect of RT treatment as recorded by patients. The mean scores of dysphasia were significantly increased in both groups as reported at the first week after RT with no significant difference between both groups, followed by improvement as reported at the later questionnaires. Patients in group A reported increased emesis in the questionnaires collected at the first week after RT.

Clinicians' reported toxicity

Nine patients in group A suffered from significant dysphagia as assessed in the first week after RT, 8 of them were grade

Table 4 Symptoms improvement as reported by physicians' assessment.

	s	Start		After 1 week	After 6 weeks	After 16 weeks	Overall improvement	
		No.	%				No.	%
Dyspnea	A	15/15	100.0	9/15	1/6	0/2	10/15	66.7
	B	14/15	99.3	6/15	3/8	0/3	9/14	64.3
	χ^2 (p)						0.144 (0.705)	
Hemoptysis	A	9/15	60.0	9/9	–	–	9/9	100.0
	B	10/15	66.7	10/10	–	–	10/10	100.0
	χ^2 (p)						–	
Cough	A	15/15	100.0	8/15	1/15	0/8	9/15	60.0
	B	15/15	100.0	10/15	0/15	0/10	10/15	66.7
	χ^2 (p)						0.144 (0.705)	
Chest pain	A	7/15	46.7	5/7	0/2	0/0	5/7	71.4
	B	10/15	66.7	7/10	0/2	0/1	7/10	70
	FEp						0.120	

χ^2 : Chi square test.

FEp, *p* value for Fisher Exact test.

II and only 1 patient suffered from grade III dysphagia, while in group B 7 patients suffered from significant dysphagia, 7 patients were grade II, while 2 patients were grade III. No spinal toxicities were detected in any of the patients of both groups. Skin toxicity was detected only in 1 patient in group A in the form of Grade I erythema which was transient and improved without treatment, skin toxicities of higher grades were not seen. Clinically vomiting after RT was transient and of grade I and relieved by the routine medications.

Health related quality-of-life

There were no statistically significant differences in the mean scores of all items between the two groups at base line and during follow up times. Except for increased emesis in the first week reported by patients in group A and decreased constipation in the sixteenth week reported by patients in group B,

there were no other differences as regards the whole questionnaire items at the follow up times.

Tumor control

Chest X-rays and/or CT chest scans obtained at 6 weeks and/or 4 months after RT for 14 patients in group A and 14 patients in group B (2 missed patients, 1 in each group), revealed no significant differences in the radiological response between both study arms, with a Complete response(CR) in only 1 patient (7.1%) in group B, a partial response(PR) in 2 patients (14.3%) in group A and 2 patients (14.3%) in group B, a minor response(MR) in 3 patients (21.4%) in group A and in 3 patients (21.4%) in group B, a stable disease(SD) in 8 patients (57.1%) in group A and in 7 patients (50%) in group B, and a progressive disease(PD) in 1 patient (7.1%) in group A and in 1 patient (7.1%) in group B. The overall response rate

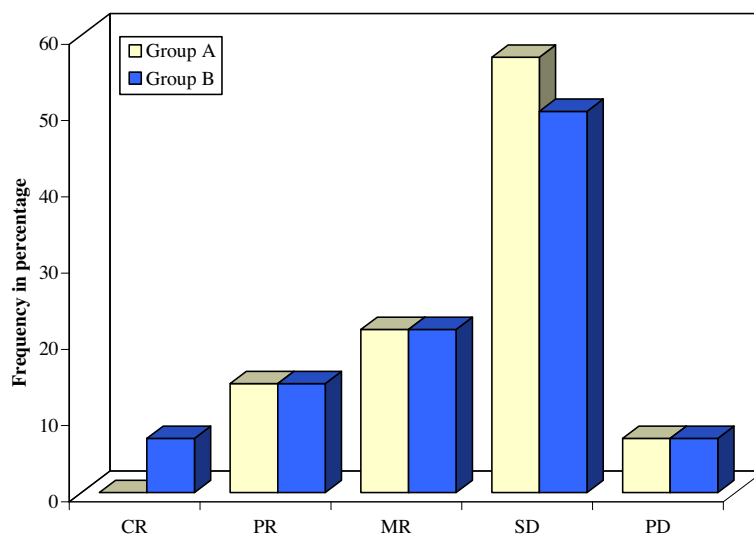


Figure 4 Comparison between the two studied groups according to response.

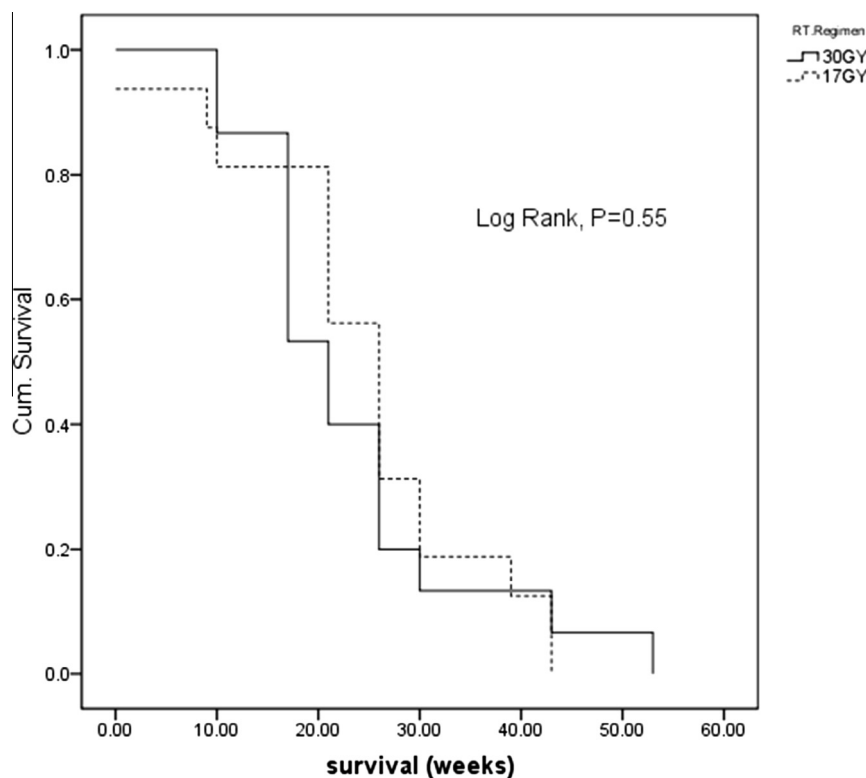


Figure 5 Kaplan–Meier’s estimate of overall survival.

was 35.7% and 42.8% in group A and group B, respectively (Fig. 4).

Overall survival

Overall survival for patients in the study revealed no significant survival difference among the two treatment groups ($P = 0.500$; Fig. 6). The median survival was 5 and 6 months in group A and B, respectively (Fig. 5):

Discussion

Although the effect of chemotherapy in advanced NSCLC in the 1980s was proven superior to the best supportive care with respect to survival, HRQOL, and symptom relief, and there has been an expanded use and increasing efficacy of novel chemotherapy regimens for this disease during recent years [11]. Still, thoracic RT remains an important treatment modality for patients with symptoms from intrathoracic disease.

The study population characteristics were homogenous between the two study groups with no statistically significant differences. The mean age was 60.93 and 59.33 years for the group (A) and the group (B). This was close to the mean age of the patients randomized in the medical research council (MRC) I study [12] which was 65 years, and that of the Norwegian study [13] which was 68 years.

The majority of patients in both groups were males 80% in group A and 93.3% in group B. This male predominance is found in almost all the previously listed studies except in the American study [14] in which females were 61% of the study population.

All cases were histopathologically proved to be NSCLC. Squamous cell carcinoma (SCC) was the most common pathological subtype in both groups followed by large cell carcinoma and adenocarcinoma, this is against the international incidence in which adenocarcinoma is the most common histopathological type of NSCLC, and this could be attributed to the small number of patients in this study which is not representative of the real incidence in the community. Moreover, most of the patients were males who smoke bad quality of cigarettes with high tar content. However, this is matching with the MRC I, the Norwegian, and the Polish [12,13] studies’ population in which SCC was also the predominate subtype.

Most of the patients incorporated in this study were stage IV disease 60% and 53.3% in group A and group B, respectively, followed by stage IIIB 26.7% and 33.3% in group A and group B, respectively. Traditionally, stage IIIA disease should be treated with a curative intent, with concurrent chemo radiotherapy followed by either surgery if gets respectable and/or chemotherapy. In our study, only patients with poor prognostic factors in stage IIIA who were not considered as candidates for any curative treatment were eligible, and those were only 13.3% of patients in both groups.

Eleven out of the 15 patients in group A had received chemotherapy before study entry as 8 of them were stage IV at the time of diagnosis but their pulmonary symptoms were still insignificant, While the 3 other patients (2 were stage III B and 1 was stage III A) were receiving induction chemotherapy and were planned to receive concomitant chemo radiotherapy but their condition progressed and their performance status worsened and became eligible to enter the study. As regards group B, 9 out of the 15 patients had received previous doses of chemotherapy as 4 of them were

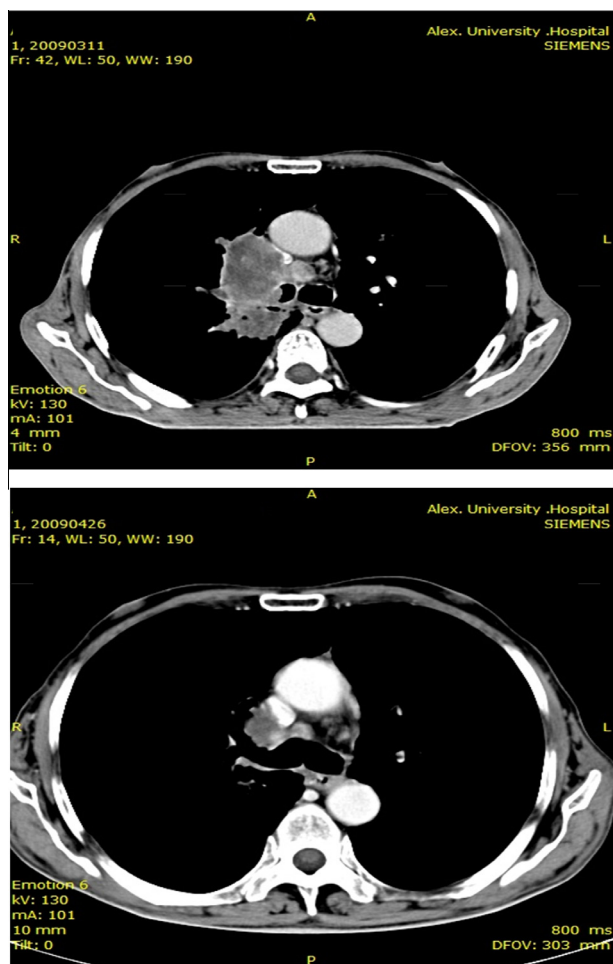


Figure 6 A case with a very good radiological response after RT.

metastatic before study entry and 5 patients (4 were stage III B and 1 was stage III A) were receiving induction chemotherapy. All of the patients in both groups had received cisplatin based chemotherapy.

Considering the poor prognosis for the patients in this study, the primary end point was the relief of symptoms caused by the intrathoracic disease, which were dyspnea, cough, hemoptysis, and chest pain, the results of our study showed that there was a significant palliation of these symptoms following RT as reported by patients and also as assessed clinically with no statistically significant difference among both groups. The modern definition of palliation (as recommended by the MRC Cancer Trials Office) encompasses symptom improvement (reduction of existing moderate or severe symptoms), control (no deterioration in mild symptoms) and prevention (no deterioration in those with no symptoms) [15]. Such a comprehensive assessment is particularly important in the setting of lung cancer, a tumor typically accompanied by multiple symptoms. The efficacy of palliative RT depends on the type of predominant symptom. Several studies demonstrated that the most effectively palliated symptoms include hemoptysis and chest pain [14]. In some studies, including the present study, RT also resulted in effective relief of cough and dyspnea [12,13].

According to the patients' reported symptom control, hemoptysis had the highest improvement rate of 100% in both

groups which is noted at the first week after RT and seemed to last throughout the planned follow up period as noted by the significant improvement of the mean scores of hemoptysis throughout the follow up period. Patients reported improvement in chest pain by 71.4% and 70% in group A and B, respectively but for a shorter period of time as noted by the increased mean scores of chest pain at week 16 after RT. Cough was improved in 66.7% and 73.3% of patients in group A and group B, respectively. While, dyspnea was palliated in 73.3% and 60% of patients in group A and group B, respectively. The palliation for both dyspnea and cough was of longer duration than that of chest pain and continued till week 16 after RT. There was no statistically significant difference in the palliation rate or degree of all symptoms among both groups.

As regards the clinicians' symptom evaluation only patients with significant symptoms at baseline were analyzed, the results coincide with those reported by patients with no major discrepancy. Again hemoptysis had the highest overall improvement in 100% of patients in both groups, followed by chest pain, dyspnea and cough with overall improvement rates ranging from 60% to 71.4% with no statistically significant difference among both study arms.

These results were in agreement with the results of the prospective randomized trials of the MRC I and II, Sundström et al., and Senkus-Konefka et al. [13,16]. All these studies showed a significant palliation of the intrathoracic symptoms after the hypo fractionated regimen of 17 Gy in two fractions, which was equal to that achieved by more protracted regimens. The palliation rate of symptoms at these studies was as follows: hemoptysis had the highest improvement that ranged from 80% to 100%, denoting the very effective hemostatic control achieved by RT, cough palliation observed in 40–83%; dyspnea in 40–75%; and chest pain in 50–80%.

These results, however, were challenged by a few studies, which demonstrated better palliation in patients given higher radiation doses [17,18]. These discrepancies can at least partially be explained by different fractionation schedules, various end points and differences in evaluation tools used in particular studies [18]. In particular, many studies emphasized the importance of relying more on patient self-assessment than on physicians' evaluation, as major differences are observed between results of both these judgments.

Induced esophagitis was the main toxicity of treatment as reported by patients and as assessed clinically as well, with no significant difference among both groups. Sixty percent of patients in both groups suffered from significant dysphasia as assessed 1 week after RT, 1 patient (6.7%) in group A and 2 patients (13.3%) suffered from grade III dysphasia that required tube feeding & IV fluids. The condition then resolved rapidly and only 20% of patients in group A and 26.7% in group B had significant dysphasia at week 6 after RT, these patients were originally suffering from dysphasia before the start of treatment due to the local compression of the tumor over the esophagus. Skin toxicity was detected only in 1 patient in group A in the form of Grade I erythema which was transient and improved without treatment, skin toxicities of higher grades were not seen. Clinically vomiting after RT was transient and of grade I and relieved by the routine medications. No cases of any grade of radiation induced myelopathy nor pneumonitis were detected in any of the patients in both arms during the follow up times. These results are in accordance with some previous randomized trials which reported

dysphagia as the main toxicity of treatment with no differences among different fractionation schedules used in these trials [12,16], while other trials reported more dysphagia in the hypo fractionated arm [19] and two trial reported more dysphagia in the more protracted regimen [20]. Spinal toxicities were reported in some studies [21] but in rare cases.

HRQOL was preserved equally in the two study arms with no significant deterioration in any domain of the EORTC questionnaires at the follow up times. The QOL was not measured in many previous randomized control trials (RCTs) [16] while it was an important endpoint in few other trials [19]. The results of these trials were contradictory with two trials reported equivalent QOL in patients treated with the hypo fractionated to those treated with the more protracted regimens [22] whereas the other two trials concluded that the higher doses give better QOL [19].

As regards the local radiographic response to RT, the overall response rate was not significantly different among both study arms (35.7% and 42.8% in group A and group B, respectively). This was close to the results of MRC I trial that showed a complete response in 7% of patients in the hypofractionated arm and 5% of the multifractionated regimen, and a partial response in 22% and 25%, respectively.

The overall survival for patients in the study revealed no significant survival difference among the two treatment groups P value = 0.550. The median survival was 5 and 6 months in group A and B, respectively. This short overall survival is not surprising given the overall poor PS of the patients, as well as that more than half of them were metastatic at treatment and about two thirds had received previous chemotherapy and progressed on it.

Our survival results are in accordance to that of the majority of the RCTs which showed no significant differences between the hypofractionated and higher dose multifractionated regimens in terms of survival [22]. The major concern related to the use of hypo fractionated treatment schedules is their potential inferiority in terms of overall survival as shown in three RCTs [19]. Some evidence exists that higher RT doses result in a modest increase in survival, although at the expense of higher acute toxicity [20]. The effect of RT dose and regimen on overall survival, if any, was in all instances limited to patients with good PS and/or relatively non advanced disease, that is, those most likely to benefit from improved local control [20]. In contrast to these results, the polish study [16] demonstrated improved survival in the shorter treatment arm. This intriguing result should, however, be interpreted with caution due to a relatively small number of patients (100 patients) in this polish study. Although in two other studies a trend toward improved survival in the lower dose group was observed in a subset analysis [23]. It seems reassuring that such a short treatment is at least not inferior in terms of survival, compared to a standard schedule.

Apart from purely medical factors, such an approach has obvious logistic and economic benefits, which is of particular importance in countries with limited health care resources. Commonly used treatment schedules are still, however, more often based on tradition than on clinical research results [18]. The sources of reluctance toward hypo fractionated regimens include the lack of experience with large single fraction, concerns about its acute toxicity and uncertainty about the appropriate patient selection for hypo fractionated RT [18].

Conclusion

Palliative RT alone plays an important role in the palliation of symptomatic intrathoracic disease and in the preservation of HRQOL, in patients who have limited expected survival time and/or intolerance to combined chemotherapy and radical RT regimens.

The short-term hypo fractionated treatment is convenient for patients with a limited expected survival. Furthermore, hypo fractionation schedules require fewer trips to the RT facility for the patient, and in all likelihood, smaller direct and indirect costs for society, especially in developing countries with limited resources.

The hypo fractionated RT regimen used in this study proved to be equally effective as the more protracted regimen in terms of palliation of the intrathoracic symptoms, treatment tolerance, HRQOL, and overall survival. This may hopefully convince at least some radiation oncologists still using more protracted regimens to adopt this simple and efficient treatment.

Conflict of interest

We have no conflict of interest to declare.

Appendix A

ECOG PS scale (Appendix I) [6]

This scale is used to measure performance of which the patient is *capable*. For example, a patient in the hospital for metabolic studies may be fully capable of performing normal activities, but will remain in bed through his or her own choice. Such a patient should be coded 0, "normal."

- 0 Fully active; no performance restrictions.
- 1 Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
- 2 Capable of all self-care but unable to carry out any work activities. Up and about > 50 Percent of waking hours.
- 3 Capable of only limited self-care; confined to bed or chair > 50 percent of waking hours.
- 4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

EORTC Quality of life questionnaire (QLQ)-C30 and the EORTC lung cancer-specific module QLQ-LC13 (Arabic versions) (Appendix II) [8]

EORTC QLQ-C30 (version 3)

نحن معنيون ببعض المعلومات عنك وعن صحتك الرجاء اجب عن كل الاسئلة بنفسك بوضع دائرة حول الامكانية الاكثر ملائمة لك لا يوجد جواب " صحيح" او "خطأ" المعلومات التي تنلى بها سوف تبقى في كامل السرية.

الرجاء املأ الحروف الاولى لاسمك:

تاريخ ميلادك (اليوم، الشهر، السنة):

(التاريخ اليوم (اليوم، الشهر، السنة):

كثير جدا	بما فيه الكفاية	قليلا	اطلاقا	
4	3	2	1	هل لديك صعوبة في بذل جهد جسماني شاق كحمل كيس مشتريات ثقيل او حقيبة؟
4	3	2	1	هل لديك مشكلة في سير مسافة طويلة؟
4	3	2	1	هل لديك مشكلة في السير لمسافات قصيرة خارج البيت؟
4	3	2	1	هل تحتاج للبقاء في السرير او المقعد خلال اليوم؟
4	3	2	1	هل تحتاج لمساعدة في الاكل ارتداء الملابس الاغتسال المراض؟
كثير جدا	بما فيه الكفاية	قليلا	اطلاقا	خلال الاسبوع الماضي
4	3	2	1	هل كنت محدودا بالقيام بعملك او فعاليات يومية اخرى
4	3	2	1	هل كنت محدودا في ممارسة هواياتك او فعاليات في اوقات الفراغ
4	3	2	1	هل ضاقت انفسك
4	3	2	1	هل كان لديك الم
4	3	2	1	هل كنت بحاجة لان تستريح
4	3	2	1	هل عانيت من مشاكل بالنوم
4	3	2	1	هل شعرت بالوهن
4	3	2	1	هل فقدت شهيتك
4	3	2	1	هل شعرت بالغثيان
4	3	2	1	هل تقيأت
4	3	2	1	هل عانيت من امساك
4	3	2	1	هل كان لديك اسهال
4	3	2	1	هل كنت تعباننا
4	3	2	1	هل الوجد شوش فعالياتك اليومية
4	3	2	1	هل كان لديك صعوبة بالتركيز في الامور مثل قراءة جريدة او مشاهدة التلفزيون
4	3	2	1	هل شعرت بالتوتر
4	3	2	1	هل شعرت بالقلق
4	3	2	1	هل شعرت بالهيجان
4	3	2	1	هل شعرت بالاكنتاب
4	3	2	1	هل كانت لديك صعوبة بتذكر اشياء
4	3	2	1	هل حالتك الجسمانية او علاجك الطبي تدخل بحياتك العائلية؟
4	3	2	1	هل حالتك الجسمانية او علاجك الطبي تدخل بحياتك الاجتماعية؟
4	3	2	1	هل حالتك الجسمانية او علاجك الطبي ادى الى مشاكل اقتصادية؟
				فى الاسئلة التالية رجاء اشر/ اشرى بدائرة حول الرقم بين 1-7 الاكثر ملاءمة لك:
				كيف تدرج/ تدرجى صحتك عموما خلال الاسبوع الماضي؟
7	6			1 2 3 4 5
ممتاز				سء جدا
				كيف تدرج/ تدرجى جودة حياتك خلال الاسبوع الماضي؟
7	6			1 2 3 4 5
ممتاز				سء جدا
يبلغ المرضى في بعض الأحيان عن إصابتهم بالأعراض التالية. يرجى الإشارة إلى الدرجة التي عانيت فيها من هذه الأعراض أو المشاكل خلال الأسبوع الماضي.				
خلال الأسبوع الماضي				
كثيرا جدا	بعض الشيء	قليلا	لا شيء	
4	3	2	1	ما هو عدد المرات التي سعلت فيها
4	3	2	1	هل سعلت دما ؟
4	3	2	1	هل شعرت بضيق في التنفس وأنت مسترخيا؟
4	3	2	1	هل شعرت بضيق في التنفس عند المشي ؟
4	3	2	1	هل شعرت بضيق في التنفس أثناء صعود السلالم ؟
4	3	2	1	هل شعرت بالتهاب في الفم أو اللسان ؟
4	3	2	1	هل شعرت بصعوبة في البلع ؟
4	3	2	1	هل شعرت بتنميل في اليدين أو القدمين ؟
4	3	2	1	هل لاحظت حدوث تساقط بشعرك ؟
4	3	2	1	هل شعرت بألم في الصدر ؟
4	3	2	1	هل شعرت بألم في الذراع أو الكتف ؟
4	3	2	1	هل شعرت بألم في الأجزاء الأخرى من جسمك
				إذا كان الرد بالإيجاب فاین.....
				هل تناولت أي دواء ضد الألم ؟
				نعم 2 كلا 1
4	3	2	1	إذا كان الرد بالإيجاب، فما هو مدى نفع الدواء ؟

Common terminology criteria for adverse events v3.0 (CTCAE) (Appendix III) [9]

Cough

Grade 0 None

Grade 1 Mild, symptomatic, non-narcotic medications only indicated

Grade 2 Moderate, symptomatic, requiring narcotic antitussive

Grade 3 Severe cough or coughing spasms, poorly controlled or unresponsive to treatment, significantly interfering with sleep or ADL

Hemoptysis

Grade 0 None

Grade 1 Mild without blood transfusion

Grade 2 Moderate without blood transfusion

Grade 3 Severe requiring transfusion

Grade 4 Catastrophic bleeding, requiring major non-elective intervention

Chest pain (Non-cardiac)

Grade 0 None

Grade 1 Mild pain not interfering with function

Grade 2 Moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living

Grade 3 Severe pain: pain or analgesics severely interfering with activities of daily living

Grade 4 Disabling

Dyspnea

Grade 0 None

Grade 1 Dyspnea on exertion, but can walk 1 flight of stairs without stopping

Grade 2 Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping

Grade 3 Dyspnea at normal level of activity (with ADL)

Grade 4 Dyspnea at rest or requiring ventilator support

Dysphagia

Grade 0 None

Grade 1 Symptomatic, able to eat regular diet

Grade 2 Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated < 24 h

Grade 3 Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 h

Grade 4 Life-threatening consequences (e.g., obstruction, perforation)

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